Learning mechanisms in fear and anxiety: It is still not what you think it is

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1. Introduction

Alex is a 24-year old male who recently dropped out of work because it became difficult to function well in his job as a communication-assistant. For example. he avoided making telephone calls in the presence of others and avoided having lunch with his colleagues. When talking to a superior in particular, Alex is extremely self-conscious and aware of certain physical symptoms such as blushing, sweating and trembling. He is afraid that others will notice these symptoms and would evaluate him as being incompetent, stupid or as being a weirdo. Alex grew up in a family of lawyers, in which the importance of a professional career was stressed very much. Alex mentions that he has always been timid, but his social anxiety became worse at university, and in particular after he gave a wrong answer on a question during class. The professor reacted by saying that he does not belong at university if he cannot answer a question which is that obvious. Alex reacted to this by running out of the classroom. He remembers that his classmates were laughing when he was running out of the room, but he is not sure whether this memory is accurate or whether he imagined it. After this incident, Alex started to skip classes and avoided contact with his classmates.

Learning experiences play a crucial role in the etiology of anxiety. An individual with social anxiety, such as in the example of Alex, might have learned that (saying something stupid in) the company of others is related to rejection and exclusion, which might have caused the current symptoms of social anxiety and avoidance to manifest itself. Learning theory has not only provided valuable insights into the onset of anxiety disorders, it has also provided and still does provide a major impetus in the development and optimization of the treatment of anxiety.

In this chapter we will discuss how learning mechanisms as investigated in basic fear conditioning research are at work in clinical fear and anxiety. We will mainly discuss research in human (healthy and anxious) participants and occasionally discuss findings from rodent

research as well. The first section of this chapter will focus on different procedures and outcomes when modeling fear acquisition in the laboratory. Subsequently, we will evaluate whether we can translate the findings from fear conditioning research in the laboratory to clinical anxiety based on three established criteria of external validity: face validity, construct validity and predictive validity. We will demonstrate that recent developments in the field can respond to often heard critiques on the classical fear conditioning model of anxiety.

2. A learning perspective on the etiology of anxiety disorders

2.1 A classical conditioning account of anxiety

One of the first and without doubt most famous case studies illustrating that fear reactions can be acquired by learning experiences is the one of Albert B. as described by Watson and Rayner (1920). A phobic reaction was induced in Albert by pairing a stimulus that initially did not evoke fear (i.e., a white rat) with an aversive outcome (i.e., a loud noise). After repeatedly presenting the rat together with the loud noise, Albert started to react fearfully to the rat. This is one of the first demonstrations of fear conditioning, nowadays an established procedure to induce fear in the laboratory.

The early demonstration of Watson and Rayner that anxiety for a stimulus can develop by learning experiences, and in particular by pairing the stimulus with an aversive event, relies on the experimental work of Pavlov (1927). Using dogs as subjects, Pavlov paired stimuli such as sounds with food intake. Pavlov demonstrated that the dogs initially did not show increased saliva production in response to the sound. However, after several pairings of the sound together with the food, the sound started to elicit increased saliva production. This is referred to as *classical or Pavlovian conditioning*. We will now use Pavlov's procedure to define the concepts involved in learning. The increased saliva production in response to the sound (CS) is called the *conditional response* (CR). A CR can be defined as a change in responding that is conditional upon the relation between the presence of at least two stimuli

(De Houwer, Barnes-Holmes, & Moors, 2013). In Pavlov's procedure, one of these two stimuli is the sound, which functions as a *conditional stimulus* (CS). Such CS can be defined as a stimulus to which responding changes conditional upon a relation with another stimulus (i.e., with the food). The food stimulus itself is termed the *unconditional stimulus* (US). In case of successful conditioning, the US changes responding to the stimulus it is related to (i.e., to the CS)[1]. Notably, in Pavlov's early experiments the US was an appetitive stimulus (i.e., food). This is different for fear conditioning research, where the US is an aversive stimulus (e.g., loud noise). However, as will become clear in the next paragraph, besides this, the procedure is fairly similar.

2.2 (Human) fear conditioning: Procedures and outcomes

The fear conditioning model is widely recognized as a model for the pathogenesis of fear and anxiety disorders (e.g., Beckers, Krypotos, Boddez, Effting, & Kindt, 2013). Typically, the CS is paired (repeatedly) with an aversive US until it elicits conditional responding indicative of fear and anxiety.

In human fear conditioning a variety of stimuli has been used as a *CS*, ranging from fairly neutral stimuli (e.g., geometrical shapes) to fear-relevant stimuli (e.g., spiders, fearful faces). Often the CS is a visual stimulus, but other modalities such as auditory and olfactory stimuli have been used as well. An electrocutaneous stimulus or electric shock is typically used in the laboratory as a *US*, with an intensity set at a level which is perceived as 'uncomfortable, but not painful' by the individual participant. However, also auditory stimuli such as human screams or (bursts of a) loud (white) noise (100-105 dB) and aversive pictures or movie clips have been used as a US (e.g., Joos, Vansteenwegen, & Hermans, 2012; Lenaert et al., 2014).

[1] Changes in responding to the US, as caused by its relation with the CS, are possible but typically left uninvestigated in conditioning research.

For modelling panic symptoms in the laboratory, CO_2- enriched air leading to a sensation of breathing restriction has proven successful (Leibold et al., 2013).

As described earlier, after pairing a CS (repeatedly) with a US, presenting the CS will elicit a *CR* indicative of fear or anxiety. Several dependent variables can be included as indices of fear and anxiety in response to the CS. Conform Lang's bio-informational theory (1979) and emotion theory (Frijda, 1986) dependent variables in fear conditioning research can focus on each of the three response systems: the verbal, psychophysiological, and behavioral level.

On the *verbal* level, US-expectancy ratings are commonly used by asking participants to indicate the extent to which they expect US-occurrence (Boddez et al., 2013). In the example of Alex, this could correspond to the extent to which he expects that others will exclude or reject him after saying something (stupid) during lunchbreak. In addition to US-expectancy ratings, ratings of subjective fear, CS valence and subjective units of distress are sometimes included.

As *physiological* indices, skin-conductance response (SCR) and fear-potentiated startle (FPS) have a long history in human fear conditioning research. In SCR (also known as galvanic skin response, electrodermal responding or sympathetic skin response) changes in the electrical conductance of the skin are measured. This is informative for fear learning because the conductive properties of the skin are influenced by sympathetic autonomic arousal and are reactive to signals of salient events. Notably, SCR is not specific for the anticipation of aversive events, but increases in response to any salient event (e.g., also appetitive ones; Lipp, 2006). In contrast to SCR, a potential advantage of FPS is that it is modulated by emotional valence (Grillon & Baas, 2003, but see Mallan, Sax, & Lipp, 2009). For measuring FPS in humans, an eye-blink reflex is elicited by the administration of a high-intensity probe of white noise (e.g., Blumenthal et al., 2005). The amplitude of this eye-blink

reflex, as measured by the electromyographic activity of the muscles around the eye (orbicularis oculi), is potentiated in anticipation of aversive events. In addition to SCR and FPS, other physiological indices of fear and anxiety, such as heart rate and pupil dilation have been included in human fear conditioning studies (e.g., Leuchs, Schneider, Czisch, & Spoormaker, 2017). Importantly, these physiological indices correspond to the physical symptoms in clinical anxiety. In the clinical example, Alex started to sweat when he was confronted with a fear-eliciting situation such as when talking to a superior, typically resulting in increased electrical conduction of the skin. In addition, his heart started pounding really fast. He also reported that, while being at the office, he had a tendency to startle each time the telephone of a colleague ringed.

A third set of dependent variables is situated on the overt behavioral level. As a key characteristic and one of the diagnostic criteria of anxiety disorders (American Psychiatric Association, 2013), *avoidance behavior* can be considered an indispensable outcome measure when modeling pathological anxiety. Alex' avoidance behavior was debilitating and prevented him to do his job appropriately. Because he was afraid of saying something stupid or making a bad impression, he avoided making telephone calls in the presence of colleagues, going to team meetings and having lunch with colleagues or superiors. Nevertheless, whereas in most fear conditioning studies typically at least one physiological and one verbal measure is included for reasons of convergent validity, only a few research groups consistently include the assessment of avoidance (tendencies) (Beckers et al., 2013). In fear conditioning research, avoidance can be measured by giving participants the option to avoid the CS (e.g., Grillon et al., 2006) or to avoid the US when presented with the CS (e.g., van Meurs, Wiggert, Wicker, & Lissek, 2014). Moreover, the avoidance response can vary in cost, ranging from button presses to avoid the US without additional response cost (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009; Vervliet & Indekeu, 2015) to avoidance responses associated with a cost,

for instance a loss in points (Pittig, Brand, Pawlikowski, & Alpers, 2014). In addition, visual avoidance (e.g., looking away) can be assessed by using eye-tracking methodology (e.g., Rinck & Becker, 2006). Some studies include a separate approach-avoidance task to assess avoidance tendencies or the urge to avoid (e.g., Krypotos, Effting, Arnaudova, Kindt, & Beckers, 2014; Krypotos, Arnaudova, Effting, Kindt, & Beckers, 2015, Van Gucht, Vansteenwegen, Van den Bergh, & Beckers, 2008). In such task, a manikin figure typically appears at the bottom or top of the screen and the CS is presented in the opposite half of the screen. Participants are instructed to move the manikin towards (approach) or away from (avoidance) the CS as quickly as possible by pressing a key or by handling a joystick. The time between the CS onset and the response is measured. If participants are faster to move the manikin away from the CS than towards it, a tendency to avoid the CS is inferred.

For reasons of cross-validation, fear conditioning studies typically include more than one dependent variable, usually a verbal measure and one or more psychophysiological measures. Importantly, correlations between outcome measures often have shown to be only weak (e.g., Hodgson & Rachman, 1974). This observed divergence in outcome measures can, apart from measurement error, also be explained by the fact that the three response systems indeed represent different and partly independent dimensions of fear and anxiety (Beckers et al., 2013).

An important question is whether (human) fear conditioning can indeed serve as a model for clinical anxiety disorders. As we discussed in the previous paragraph, at a procedural level and with regard to outcome measures the fear conditioning model shows some clear similarities with the pathogenesis and symptomatology of clinical anxiety. In the next paragraph, we will evaluate the validity of human fear conditioning as a model for clinical anxiety disorders in a more systematic way.

2.3 The external validity of the (human) fear conditioning model

It is considered one of the most important advantages of (human) fear conditioning research that it allows modelling pathological behavior in healthy subjects. A main assumption is that the knowledge and insights acquired through highly controlled fear conditioning experiments can inform clinical practice. This assumption concerns the external validity of the fear conditioning model. In the past, several critiques have been formulated on this model, arguing that it might be too simplistic to capture the complexity of clinical anxiety. Mineka and Zinbarg (2006) replied to these critiques and illustrated how contemporary approaches of conditioning and learning theory can overcome a substantial part of them. Below, we further elaborate on the work of Mineka and Zinbarg (2006) by providing a systematic evaluation of the fear conditioning model using three established criteria of validity: face validity, construct validity and predictive validity[2]. These criteria have been used to evaluate external validity in pharmacological and more recently in behavioral research (Davey, 2017; Luyten, Vansteenwegen, van Kuyck, Gabriëls, & Nuttin, 2011; Scheveneels, Boddez, Vervliet, & Hermans, 2016; Vervliet & Raes, 2013).

2.3.1 Face validity

The most straightforward validity criterion is face validity. This refers to the surface similarity between the (fear conditioning) model and the (anxiety) disorder. As discussed in the previous section, at face value, the fear conditioning model shows important similarities with clinical anxiety. Conditional reactions that are observed in fear conditioning studies such as SCR, startling, elevated heart rate, correspond to the physical reactions in real-life fear-eliciting situations. In addition, (a tendency) to avoid the conditional stimulus as well as the expectancy that the aversive outcome will occur can be observed in both fear conditioning studies and clinical anxiety.

[2] The reader may note that the subtitle of our chapter ("It is still not what you thought it was") is similar to the subtitle used in the article of Mineka and Zinbarg (2006).

Notably, fear conditioning research in the laboratory typically uses simple, unimodal stimuli such as geometrical shapes, whereas in real-life the learning experiences often take place in more complex circumstances. Therefore, more recently, the use of complex, multi-sensory stimulus configurations (e.g., auditory, tactile, olfactory, visual) has been proposed to provide a better analogue for real-life experiences (Waters, LeBeau, & Craske, 2017). Virtual and augmented reality might be a useful technology to achieve this (e.g., Baas, Nugent, Lissek, Pine, & Grillon, 2004). However, the added value of using these more complex stimulus configurations still requires empirical testing. More specifically, future research should reveal whether using more complex stimulus configurations (as compared to simple stimuli) allows for better translation to clinical anxiety with respect to, for example, newly proposed treatment strategies.

Establishing and optimizing the face validity of the fear conditioning model can be considered a first step, but it is not the most decisive criterion of external validity. In the next paragraph we will continue with evaluating more significant criteria.

2.3.2 Construct validity

The evaluation of the construct validity revolves around the question whether the same (etiological) processes are at play in the model and the clinical disorder. Different from face validity, construct validity is not about a first impression, but about underlying mechanisms.

A first indication for similar (neurobiological) processes underlying the fear conditioning model and clinical anxiety can be found in neuroimaging studies that reveal a similar neurocircuitry involved in anxiety patients and in fear conditioning in animals and healthy humans (e.g., Sehlmeyer et al., 2009). In particular, a central role of amygdaloid nuclei has consistently been demonstrated in the acquisition and expression of fear responses and across different anxiety disorders (e.g., Kent & Rauch, 2003; Sehlmeyer et al., 2009; Shin & Liberzon, 2010). In addition, other brain areas such as the hippocampus, insula, anterior

cingulate cortex and ventromedial prefrontal cortex have been identified as regions of interest across anxiety disorders and in fear conditioning research (e.g., Damsa, Kosel, & Moussally, 2009; Etkin & Wager, 2007; Ipser, Singh, & Stein, 2013)[3].

An assumption of the conditioning approach is that learning processes underlie the etiology and treatment of clinical anxiety. Early learning theorists such as Watson used simple acquisition procedures to model the etiology of anxiety disorders. In these procedures one neutral stimulus (e.g., a white rat) was paired with one aversive outcome (e.g., a loud noise). This simple acquisition procedure has been subject to some important critiques. We will discuss some of these earlier shortcomings as well as how they are addressed by more recent developments in learning theory.

2.3.2.1 A contemporary learning theory approach on the etiology of anxiety disorders

One criticism that has been formulated on the conditioning perspective is *that many anxiety patients are not able to report a CS-US event that can account for the current anxiety symptoms*. A first possibility to nonetheless explain this from a learning account is to simply assume that a CS-US event has occurred, but that people are not accurate in remembering and retrospectively reporting this conditioning experience (Merckelbach, van den Hout, Hoekstra, & de Ruiter, 1989; Öst & Hugdahl, 1981).

Alternatively and maybe more likely, generalization and higher order conditioning might obscure learning as the actual cause of the anxiety symptoms. Generalization will be discussed in more detail below but can already be illustrated by an anecdote about Albert from the study by Watson and Rayner (1920). It was said that Albert did not only fear white rats after the conditioning experience, but also women wearing fur coats. If Albert would have entered treatment with this complaint, one might have speculated about the sensational (Freudian) origins of this fear. Nonetheless, it can easily be explained by a learning account if

[3] Results regarding these areas are less univocal and their role remains subject of discussion (e.g., Maren, 2008; Sehlmeyer et al., 2009).

one assumes that the fear generalized from the rat to fur coats based on their looking alike. With respect to higher order conditioning, emetophobia (i.e., fear of vomiting) may serve as an example. Although some dry foods (e.g., cereal without milk) might never have been directly involved in an aversive learning experience, the patient might relate these foods to difficulties to swallow, which in turn is related to vomiting (Bouman & van Hout, 2006). This allows to explain fear and avoidance of these foods from a learning perspective.

As discussed above, conditioning can be defined as a change in responding due to a relation in the presence of stimuli (De Houwer et al., 2013). Importantly, this definition also covers observational learning (e.g., Cameron, Roche, Schlund, & Dymond, 2016). Take the example of a patient who developed dog phobia after observing somebody else get bitten by a dog. Crucially, in such case, the fear can still be explained by (an observed) relation between the presence of stimuli; more precisely, by a relation between the presence of a dog and a dog bite. In addition, one might develop dog phobia if one is told that dogs cause bit wounds. In such fear learning via instruction, the fear is caused by a verbal description of the relation between the presence of stimuli. Accounting for learning via observation and instruction of course significantly increases the explanatory territory of the learning framework. Olsson and Phelps (2004) compared fear acquisition through direct pairings, instructions and observational learning in an experimental study with human participants. In the Pavlovian (direct) learning group, a CS was paired with an electric shock. The observational-learning group observed a confederate that was presented with the CS paired with shock. Participants in the instructed-learning group were given verbal instructions about the CS being followed by shock. Interestingly, similar levels of conditional fear responding, as measured by the skin-conductance response, were found for all three pathways. Moreover, in follow-up studies, it has been demonstrated that the neural correlates of direct and indirect pathways to fear acquisition are largely overlapping, with amygdala activation observed in both pathways

(Olsson, Nearing, & Phelps, 2007; Phelps, Connor, Gatenby, Gore, & Davis, 2001). These results provide experimental evidence that learning processes can be involved even when no direct conditioning experience is reported by the patient (also see Rachman, 1977).

Another reason why patients may not be able to report a CS-US event that can account for their anxiety symptoms is that USs may be more subtle than the bite of an animal. For example, in patients suffering from chronic fatigue syndrome something as subtle as experiencing fatigue may function as a US. If such patients learn a relation between stair climbing and fatigue, stair climbing may come to elicit fear (Lenaert, Boddez, Vlaeyen, & van Heugten, 2018). In the case of such subtle USs, it is easy to overlook that learning is involved. A similar argument holds for other interoceptive USs like panic (Bouton, Mineka, & Barlow, 2001).

Until now, we discussed how learning theory can handle the observation that many anxiety patients are not able to report a CS-US event that can account for their anxiety symptoms. Another intriguing observation which learning theory has to account for is that *not everyone undergoing a traumatic event will eventually develop an anxiety disorder* (Poulton & Menzies, 2002). Although about 95% of people experience one or more traumatic events during their lifetime, only 10-30% develops an anxiety disorder (Engelhard, van den Hout, & McNally, 2008). One can make this insightful by assuming that there are additional variables that moderate the learning process. Such variables include *temperamental/biological vulnerabilities* as well as inter-individual differences in *contextual/experiential factors before, during and following the conditioning experience*. In the following paragraphs a selection of these variables will be discussed. For a more comprehensive overview, we refer the interested reader to Lonsdorf and Baas (2015) and Lonsdorf and Merz (2017).

Given the same conditioning experience, some individuals are more vulnerable to develop an anxiety disorder than others, due to moderation by individual differences in genetic

predisposition and temperamental factors. So far, among the most established genetic factors identified as being related to anxiety problems, is a polymorphism in the serotonin transporter gene promotor region, 5-HTTLPR[4] (e.g., Lonsdorf & Kalisch, 2011). In particular, carriers of the 5-HTTLPR s-allele have found to suffer from more severe panic symptoms and social anxiety (Lonsdorf et al., 2009; Miu, Vulturar, Chis, Ungureanu, & Gross, 2013; but see Blaya, Salum, Lima, Leistner-Segal, & Manfro, 2007). The 5-HTTLPR s-allele has found to be associated with anxiety-related personality traits as well (Munafò et al., 2009). In addition, it has been demonstrated consistently that the low-efficacy 5-HTTLPR s-allele is associated with facilitated fear conditioning (e.g., Bauer, 2015; Lonsdorf et al., 2009; Wendt et al., 2014). Importantly, in line with a diathesis-stress model of psychopathology, 5-HTTLPR genotype has found to interact with stressful life events. Klucken et al. (2012), for example, found that carriers of the 5-HTTLPR s-allele showed elevated activity in the neural fear network in response to a CS, but only if they had a history of stressful life events.

In addition, particular *personality traits* might moderate the relation between learning and anxiety. An extensive set of personality traits has been investigated in this context. Among the most common studied measures is *intolerance of uncertainty (IU)*. Individuals scoring high on IU react negatively to uncertain situations and consider such situations as threatening (e.g., Carleton, 2016; Lonsdorf & Merz, 2017). Available evidence shows that IU is a transdiagnostic risk factor for the development and maintenance of anxiety disorders (e.g., Gentes & Ruscio, 2011; McEvoy & Mahoney, 2012). In some fear conditioning studies, IU has been found to be positively correlated with fear responding and generalization (e.g., Chin, Nelson, Jackson, & Hajcak, 2016; Morriss, Macdonald, & van Reekum, 2016; Nelson, Weinberg, Pawluk, Gawlowska, & Proudfit, 2015). Notably, these results were only observed

[4] Importantly, the field of genetics in psychopathology is characterized by several pitfalls and limitations such as small effects, post-hoc testing, underpowered studies and failed replications. We refer the interested reader to Dick et al., (2015), Duncan & Keller (2011) and Tabor, Risch, and Myers (2002) for a more elaborate discussion of this topic.

under conditions in which the aversive US (i.e., an electric shock) followed on 50% of the trials (Chin et al., 2016). These results confirm that individuals high on IU show stronger fear responding in ambiguous situations. Other studies, however, have failed to replicate these findings (e.g., Arnaudova et al., 2013).

In addition, contextual factors *before*, *during*, or *after* the crucial conditioning event can moderate the outcome of it by either protecting the individual against developing an anxiety disorder or by making the individual more vulnerable. Therefore, it seems important to take into account the entire learning history when trying to explain why some individuals do and some do not develop an anxiety disorder even though experiencing the same trauma. We will now demonstrate that these contextual factors fall within the scope of learning theory as well.

If an individual has safe experiences with the CS *prior to* conditioning, this can attenuate the development of a CR. For example, if a tone is first repeatedly presented by itself and in a second phase presented together with electric shock, then fear will develop slower as compared to when pre-exposure to the tone did not happen. In learning theory, this phenomenon is referred to as latent inhibition (Lubow & Moore, 1959). Similarly, it has been shown that non-traumatic experiences with the event or stimulus prior to trauma (e.g., visiting the dentist) is protective against the development of psychopathology (e.g., dental phobia) (Kent, 1997). On the other hand, pre-existing stress or trauma can make an individual more vulnerable for developing an anxiety disorder following a conditioning event. In a study by Rau, Decola, and Fanselow (2005), rats were exposed to a very mild electric shock in a specific cage (say cage B). Importantly, the experimental group received 15 heavy shocks in a very different cage in advance (say cage A), whereas the control group did not undergo this additional treatment. At test, rats in the experimental group behaved very fearful in cage B (more so than rats in the control group), even though they had only received a mild shock in this cage. This might serve to explain why posttraumatic stress disorder (PTSD) patients or

individuals with already increased stress levels are more sensitive to develop new anxieties after a mild aversive event. In the example of Alex, having bad experiences in social situations in the past (e.g., being bullied as a child) could have made him more vulnerable to develop social anxiety after the incident with the professor.

During conditioning or the traumatic event, having a sense of control or mastery might be a protective factor. Mineka, Cook, and Miller (1984) presented one group of rats with unsignaled escapable shocks and another group of yoked subjects with the same amount of unsignaled but – crucially – inescapable shocks. The group that could not escape the shocks showed more freezing to both the conditioning context and cue than the group that could escape the shock. Similar results have been found in humans by Meulders et al. (2012). Participants that had control over the offset of the US showed less conditional responding than a group of participants that had no such control. Almost immediately after Alex gave the wrong answer, he realized that he had misunderstood the professor's question. Alex could have felt more control or mastery if he had replied to the professor's nasty remark with a joke or even with a simple statement that he had misunderstood the question. Instead, he panicked and ran out of the room.

Finally, contextual variables *after* conditioning can moderate whether or not a learning experience results in clinical anxiety. In learning theory, a phenomenon referred to as US-inflation has been described: The isolated presentation of a strong US after a conditioning experience with a mild US can result in an increase in conditional fear responding (Rescorla, 1974). For example, having a severe panic attack after having experienced mild panic in an elevator might strengthen fear responding to the elevator even if the severe panic attack did not occur in the elevator. Importantly, the inflation effect can also be installed by providing verbal information about the US (e.g., den Hollander, Meulders, Jakobs, & Vlaeyen, 2015). For instance, an individual can initially experience only limited driving anxiety and avoidance

after a car accident. However, verbal threat information about the potential consequences of the accident by others afterwards might increase fear responding and avoidance. Similarly, Alex' parents, attaching much importance to a professional career, responded to the incident by saying that he will definitely not be able to pursue a career at a university following such negative remark from the professor.

In addition, repeatedly thinking or ruminating about the traumatic event can make an individual more vulnerable for developing an anxiety disorder. In particular, worrying or ruminating about the conditioning experience might result in repeated activation of the CS-US contingency which might strengthen and retain the fear memory. Joos, Vansteenwegen, and Hermans (2012) investigated this in a human fear conditioning study. In an acquisition phase, participants learned two CS-US contingencies. Both CSs were pictures of faces, the USs were a human scream and a burst of white noise. Participants were instructed to rehearse one of these contingencies in an experimental session and during the subsequent week. More precisely, they were asked to "think back to the picture (CS), the scream/noise (US) and the relationship between them". When tested with both CSs one week after acquisition, it was found that fear responding was better retained for the contingency that was rehearsed than for the non-rehearsed contingency. Importantly, these results could not be explained by merely rehearsing the CS or by increasing the negative value of the US representation (i.e., US-inflation; Davey & Matchett, 1994). In a follow-up study by Joos, Vansteenwegen, Vervliet, and Hermans (2013), rehearsal of the CS alone failed to produce sustained responding. Moreover, in Joos et al. (2013) two CSs were paired with the same US. Whereas changes in the US-representation would impact both CSs similarly, it was found that only the CS from the rehearsed CS-US contingency resulted in sustained responding. This indicates that the CS, US and the contingency between them have to be rehearsed in order to obtain the effect. Taken together, this set of experiments provides another explanation of why not everyone

undergoing a traumatic event will eventually develop an anxiety disorder: Rumination moderates the outcome of the learning process, in such way that rumination increases the risk.

2.3.2.2 More complex procedures to model the acquisition of fear and anxiety

Early learning theorists such as Watson used simple acquisition procedures, in which one neutral stimulus was paired with one aversive outcome, to model the etiology of anxiety disorders. This simple acquisition procedure has been subject to some important critiques. In the previous section, we discussed how a learning theoretical account can overcome this criticism and expand its explanatory territory by including phenomena that moderate the learning process. In this section, we will introduce a set of complex learning procedure that further add to the construct validity of the fear conditioning approach. More precisely, we will discuss three procedures that mimic important but underappreciated processes underlying anxiety disorders: (1) context conditioning, (2) inhibitory conditioning, and (3) generalization[5].

In a typical *context conditioning* procedure, a CS is paired with a US (i.e., simple acquisition procedure) in a control group, whereas the experimental group receives USs that are presented explicitly unpaired with the CS (e.g., Grillon & Davis, 1997). As a result of these unpaired CS-US presentations, the context (rather than a discrete CS) indicates that the US might occur somewhere in the not too distant future. Note that context in these experiments is typically operationalized as a background picture or color on the computer screen that stretches out in time before and after CS and US presentation (although other operationalizations have been used as well; Boddez et al., 2014). Context conditioning typically results in a sense of unpredictability and in a generalized and sustained state of arousal, because participant cannot precisely predict when the US will occur (e.g., Grillon, 2002; Grillon, Baas, Lissek, Smith, & Milstein, 2004).

[5] For a more elaborate review of complex conditioning procedures, we refer the interested reader to Boddez, Baeyens, Hermans, and Beckers (2014).

Context conditioning has been proposed as a model for pathological conditions that are characterized by chronic, future-oriented (anticipation) anxiety, such as generalized anxiety disorder (e.g., Luyten, Vansteenwegen, van Kuyck, & Nuttin, 2011). In addition, context conditioning might also explain agoraphobic avoidance often observed in individuals with panic disorder (e.g., Craske, Glover, & DeCola, 1995; Gorman, Kent, Sullivan, & Coplan, 2000). In particular, uncued panic attacks might serve as USs that are not predicted by discrete cues but merely occur in a particular context (e.g., a supermarket). As a consequence, people might come to avoid the entire context and related contexts (e.g., crowded places), engaging in generalized avoidance. Therefore, one component in the treatment of panic disorder is to identify discrete exteroceptive and interoceptive cues that are predictive for panic attacks (Craske & Barlow, 2008). Fonteyne, Vervliet, Baeyens, and Vansteenwegen (2009) provided experimental evidence for the importance of this treatment component. They used a context conditioning procedure in which both groups received predictable shocks (i.e., paired with a discrete CS) in context A and shocks that were presented unpaired with a discrete CS in context B. As predicted, higher contextual fear was observed in context B as compared to context A. To investigate whether increasing the predictability of the US would reduce contextual fear, in a subsequent phase the shocks were signaled by a novel discrete CS in context B. Results showed that this intervention led to a reduction of contextual fear and therefore confirm that increasing predictability can decrease contextual fear.

A second set of complex conditioning procedures relates to discriminating between danger and safety. In real-life, the ability to discriminate between stimuli that signal danger and stimuli that indicate the absence of danger can be considered highly adaptive. For instance, the symptoms of a panic attack might resemble a life-threatening heart attack or a stroke, but are in fact innocuous (Haddad, Pritchett, Lissek, & Lau, 2012). Responding to a

panic attack as if it is a heart attack or a stroke, leads to unnecessary escape and avoidance and an inefficient use of resources. The ability to discriminate between danger and safety cues can be modelled in a *differential inhibition* procedure, in which one stimulus (CS+) is paired with an aversive outcome, whereas another stimulus (CS-) predicts the absence of an aversive outcome. Using this procedure, elevated fear responding to safe stimuli (CS-) and impaired discrimination between danger and safety cues have been found in individuals with subclinical levels of anxiety (e.g., Ganzendam, Kamphuis, & Kindt, 2013; Haddad et al., 2012) and in patients with clinical anxiety (Duits et al., 2015; Lenaert, Boddez, Vervliet, Schruers, & Hermans, 2015; Lissek et al., 2005; Lissek et al., 2009). This suggests that the differential inhibition procedure taps into a process that is relevant to anxiety disorders and therefore has construct validity. Nonetheless, it should also be mentioned that some fear conditioning studies failed to find an effect of trait anxiety or observed an effect in only one of the outcome measures but not in the other(s) (e.g., Kindt & Soeter, 2014; Torrents-Rodas et al., 2013).

Other procedures have been used to examine impairments in safety learning. One of them is the *conditioned inhibition procedure*, a procedure known from the animal literature. In intermixed trials, one stimulus A is paired with the US, but when this stimulus is presented together with another stimulus B the US is omitted. This procedure corresponds to the use of safety signals in clinical practice. For example, an individual with driving phobia might be fearful of driving on a highway (A), but feel safe when accompanied with a fellow passenger (AB). Here as well, it has been found that high anxious individuals show higher fear responding to the safe AB stimulus compound than low anxious individuals (Chan & Lovibond, 1996; Grillon & Ameli, 2001).

A third defining feature of anxiety disorders is *stimulus generalization*. Boddez, Bennett, van Esch, and Beckers (2017) proposed to speak of generalization when a stimulus

elicits a response due to a learning experience in which that stimulus as such was not featured. As an example, consider a child experiencing painful skin burns upon touching the stove in one's grandparents' place. Behaving cautious around not just this but any stove will prevent the child from acquiring additional skin burns. In anxiety disorders, however, fear responding typically spreads to a range of stimuli and situations that are not dangerous (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Hermans, Baeyens, & Vervliet, 2013). An individual suffering from dog phobia, for instance, will typically not only react with intense fear to the specific dog involved in the biting incident (who has proven to be dangerous), but to each and every dog.

In *perceptual stimulus generalization*, the fear responding is elicited by stimuli that share perceptual similarity with the original CS+ (Kalish, 1969; Lissek et al., 2010). The example of the person suffering from dog phobia discussed above can be considered an example of perceptual generalization. In a fear conditioning paradigm, Lissek et al. (2008) investigated perceptual generalization by presenting small and large sized circles as CS+ and CS- respectively, counterbalanced across participants. Subsequently, perceptual generalization of fear responding was tested by presenting participants with circles that ranged in size between the CS+ and CS- (i.e., generalization stimuli). This generated a generalization gradient, with stronger fear responses to stimuli that resemble the CS+ and decreasing responding with decreasing similarity. Using this procedure, relatively stronger responding to the generalization stimuli (GSs) has been observed in patients with panic disorder (Lissek et al., 2010), generalized anxiety disorder (Lissek, et al., 2014) and post-traumatic stress disorder (Lissek & Grillon, 2012) compared to healthy controls. Taken together, this suggests that the generalization procedure seizes a mechanisms that is relevant to anxiety disorders and therefore is construct valid.

It is important to note that perceptual generalization can also involve interoceptive CSs (Dymond et al., 2015; Lissek et al., 2010; Schroijen & Pappens, 2015). In a patient suffering from panic disorder, fear responding might be elicited not only by the interoceptive symptoms that directly preceded and accompanied the first panic attack (e.g., tight chest), but also by other physical symptoms (e.g., full stomach after overeating).

In addition to these different forms of perceptual generalization, fear responses can also generalize across stimuli that diverge greatly in perceptual features, based on nonperceptual grounds such as categories and conceptual knowledge (e.g. Dunsmoor & Murphy, 2015). Alex not only avoided going to the class of the specific professor that was involved in the incident, he also skipped other classes and started to avoid all kinds of (social) situations including going to activities of the student club and meeting new people. Although these situations might clearly differ from the original learning experience with regard to their physical characteristics, they can be considered part of an idiosyncratic category of situations in which Alex considers himself at risk of saying something stupid and being rejected by others. This type of generalization is called *nonperceptual-based generalization* (Dymond et al., 2015).

As an experimental illustration, Dunsmoor, Martin, and LaBar (2012) presented participants with a heterogeneous collection of images of animals and tools. Images of one of these categories (e.g., animals) served as the CS+ category and were paired with an electric shock, the other stimulus category (e.g., tools) was never reinforced (i.e., CS- category). Subsequently, they tested for the generalization of fear to new stimuli stemming from the CS+ and CS- category. Results indicated higher fear responding, as measured by shock expectancy and skin-conductance response, to stimuli stemming from the CS+ category compared to stimuli from the CS- category. These results suggest that fear can generalize based on categorical and conceptual knowledge. However, this paradigm using stimuli from preexisting

categories does not allow to rule out the potential influence of perceptual similarity on the generalization of fear. It can indeed be argued that all stimuli of one category (e.g., animals) share more perceptual similarity with each other than with stimuli from the other category (e.g., tools).

To completely rule out the potential influence of perceptual overlap, research has been conducted using de novo categories by inducing concept-like relations between arbitrary stimuli in an experimental way. Vervoort, Vervliet, Bennett, and Baeyens (2014) investigated the generalization of fear acquisition within novel arbitrary categories by first creating two four-member stimulus equivalence categories (i.e., A1-B1-C1-D1 and A2-B2-C2-D2). This was done using a matching-to-sample task. Stimuli were arbitrary line drawings. In the matching-to-sample task, a sample stimulus was presented together with two comparison figures and participants were instructed to choose the comparison figure that matched the sample stimulus. After every trial participants received feedback on whether or not their response was correct. Next, one member of the first category (B1) was presented repeatedly with an electric shock, whereas the member of the second category (B2) was never paired with shock. In a subsequent test for generalization in which C1, D1, C2 and D2 were presented, it was found that conditional fear responses generalized to other members of the arbitrary category (i.e., C1, D1). These results confirm that fears can generalize across conceptually-related in addition to perceptually-related stimuli.

Finally, Boddez et al. (2012) used a blocking procedure to assess fear generalization. In the first stage of the experiment, a CS was paired with a US. In a subsequent phase, a second CS was presented in compound with the first CS. This compound was paired with the same US as in the first phase. The newly added second CS therefore did not provide any information about the onset of the US over and above the information provided by the first CS. Interestingly, high trait anxious participants showed higher fear responding when this

second CS was presented by itself at test. Such deficit in blocking might explain why certain individuals are more prone to develop clinical anxiety. A soldier might, for example, have experienced a bomb attack preceded by different cues such as a screaming colleague warning for the attack, a sandy surface, and fire of the bombing raid. A deficit in blocking would imply that the soldier, after his mission, does not only experience anxiety when a colleague is warning for another bomb attack (i.e., the most informative cue), but also when he is invited to a barbecue (fire) or when visiting the beach (sand).

In summary, we discussed complex learning procedures that allow to mimic specific processes at play in anxiety disorders. As such, these procedures add to the construct validity of the fear conditioning approach.

2.3.2 Predictive validity

Arguments about theoretical processes notwithstanding, an important question remains whether the fear conditioning model allows for translation to real life situations that pertain to clinical anxiety. This concerns the predictive validity of the fear conditioning model and will be discussed now. Two aspects of predictive validity can be distinguished (Scheveneels et al., 2016). A first aspect refers to whether environmental variables exert a similar influence in the fear conditioning model and in real life situations. A second aspect concerns testing whether a factor at the level of the individual exerts such similar influence as well. Both aspects are about the question of whether a factor, be it an environmental intervention or at the level of the individual, moderates the relation between learning experiences and fear in the lab in the same way as the relation between aversive experiences and anxiety symptoms in real life.

2.3.2.1 Do interventions have a similar effect in the fear conditioning model and in real life?

With regard to the first aspect of predictive validity, presenting the CS without US following fear conditioning is known to result in a decrease in fear responding (e.g., Hermans, Craske, Mineka, & Lovibond, 2006). This procedure is termed fear extinction. Interestingly, in real life a similar intervention also results in a decrease in fear responding, thus adding to the predictive validity of the fear conditioning account. Indeed, exposure therapy or the repeated and systematic confrontation with the feared stimulus or situation without occurrence of the expected aversive outcome is the (psychological) treatment of choice in anxiety (e.g., Cusack et al., 2016; Öst, Havnen, Hansen, & Kvale, 2015, Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008). During treatment, Alex was exposed to those social situations in which he expected to be rejected by others, such as making telephone calls when his colleagues are in the same room, meeting new people at parties, returning things to shops, etc. After repeated confrontation with these situations, Alex reported to experience less anxiety.

In addition, experimental research has demonstrated that fear responding can return after (partial or complete) fear extinction (Rachman, 1989, Vervliet, Craske, & Hermans, 2013). In clinical practice, a return in fear responding is unfortunately not uncommon either. It is estimated that 19-62% of clients experience at least some return of fear after exposure-based treatment (Craske & Mystkowski, 2006). Interesting for our present purposes, the interventions that cause a return of fear after extinction in experimental conditioning studies correspond to pathways to return of fear in real life. This again vows for the predictive validity of the model (Vervliet et al., 2013). We will now discuss the most well-studied pathways to return of fear: spontaneous recovery, (context) renewal, and reinstatement.

In the laboratory return of fear can occur when a time interval is introduced after extinction. This phenomenon has been described by Pavlov (1927) as *spontaneous recovery* and has been established in multiple laboratory studies (e.g., Huff, Hernandez, Blanding, & LaBar, 2009; Norrholm et al., 2008). Spontaneous recovery in the lab corresponds to the

clinical observation that due to the mere passage of time after exposure treatment a client can show a reappearance of fearful responding (e.g., Mystkowski, Craske, Echiverri, & Labus, 2006; Vasey, Harbaugh, Buffington, Jones, & Fazio, 2012).

A second manipulation that causes return of fear and has been investigated in fear conditioning research is a change in (background) context between extinction and a subsequent test phase. This is referred to as (contextual) *renewal* (e.g., Bouton, 2002; Effting & Kindt, 2007; Vervliet, Baeyens, Van den Bergh, & Hermans, 2013). Typically, if CS-US pairings during acquisition take place in context A and fear is extinguished in context B, return of fear responding is observed if the CS is presented in the acquisition context A (ABA renewal) or in a novel context C (ABC renewal) (Bouton & Bolles, 1979). In clinical practice, this corresponds to a relapse after successful treatment when the feared object or situation is encountered outside the treatment context. Mystkowski, Craske, and Echiverri (2002) investigated return of fear after a context change in a sample of spider-anxious individuals. All participants received a 1-session exposure-based therapy in which they were exposed to a spider in one particular context. Fear responding to the spider was tested one week later in the treatment context as well as in a novel context. Significantly higher fear responding was observed in the novel context as compared to the treatment context. Importantly, also the therapist can be considered as a contextual factor: Being confronted with the feared stimulus or situation in the absence of the therapist after (successful) treatment can result in a return of fear responding (Rodriguez, Craske, Mineka, & Hladek, 1999). Based on these findings, extinction in multiple contexts has shown to reduce renewal in the laboratory (e.g., Bandarian-Balooch, Neumann, & Boschen, 2012). Similarly, exposing a patient to the feared stimulus in multiple contexts during clinical treatment (e.g., in the treatment context, at home etc.) can attenuate return of fear responding (e.g., Olatunji, Tomarken, Wentworth, & Fritsche, 2017; Vansteenwegen, Vervliet, Hermans, Thewissen, & Eelen, 2007).

A third intervention to induce return of fear is *reinstatement*. This refers to a return in fear responding due to unsignaled US-presentations after extinction (Haaker, Golkar, Hermans, & Lonsdorf, 2014; Hermans et al., 2005). Reinstatement can be seen as the equivalent of a return of fear after unsignaled panic attacks or if the previously feared stimulus is encountered after a stressful event or in a distressing situation. After successful treatment, Alex experienced a short-term recurrence of social anxiety after someone commented him about his blushing face.

A similar argument can be made with regard to pharmacological interventions for anxiety. If the fear conditioning model has predictive validity, a pharmacological intervention that has shown to effectively reduce clinical anxiety, should exert a similar effect in the fear conditioning model. Amongst the leading pharmacological interventions for anxiety are benzodiazepines (e.g., Offidani, Guidi, Tomba, & Fava, 2013). In the fear conditioning model, there is evidence that contextual fear (but not CS-specific fear) can be reduced by benzodiazepines such as alprazolam (Baas et al., 2002; Grillon et al., 2006). These results suggest that more complex learning procedures such as context conditioning are more useful to test the clinical utility of anxiolytic interventions compared to the simple acquisition procedure.

2.3.2.2 Do factors at the level of the individual have a similar effect in the fear conditioning model and in real life?

This aspect of predictive validity concerns testing whether a factor at the level of the individual moderates the relation between learning experiences and fear in the lab in the same way as the relation between learning experiences and anxiety in real life.

In a longitudinal design, Lenaert et al. (2014) tested whether generalization and discrimination learning in a human fear conditioning procedure could predict subclinical levels of anxiety at 6-months follow-up. A large sample of first year students completed a

differential inhibition procedure followed by a generalization test. US-expectancy ratings were used as the outcome measure. Lenaert et al. (2014) argue that first year students are particularly interesting because the transition to university is accompanied by a set of real-life aversive experiences related to academics, finances, social interaction, and other issues. Crucially, students who showed deficiencies in discriminating between the CS+ and CS- in the differential inhibition procedure (i.e., impaired safety learning) reported higher levels of anxiety at 6-month follow-up. In addition, elevated responding to the generalization stimuli closer to the CS- predicted higher levels of anxiety at follow-up. These findings suggest that these complex conditioning procedures have predictive validity. More precisely, it seems that the way in which characteristics of the individual affect the effect of aversive experiences on fear expression is the same in the laboratory as in real life.

In other studies, soldiers and firemen were used as subjects. The logic underlying these studies was the same: to assess whether individuals react similarly to aversive learning experiences in the lab as they do in real life. Needless to say, soldiers and firemen are confronted with a plethora of aversive learning experiences, making this an interesting population. Sijbrandij, Engelhard, Lommen, Leer, and Baas (2013) found that impaired safety learning in the lab was associated with PTSD symptoms at 2 and 9 months post-deployment to Afghanistan. Similar findings were reported by Lommen, Engelhard, Sijbrandij, van den Hout, and Hermans (2013) and by Acheson et al. (2015). Guthrie and Bryant (2006), on their turn, found that deficits in extinction learning in the lab are a risk factor for PTSD symptoms after trauma exposure in firemen.

In conclusion, performance in the fear conditioning model allows to predict (sub)clinical levels of anxiety, pointing towards a key role for conditioning in (clinical) anxiety. Importantly, this paves the way for targeted prevention in individuals who are at relatively higher risk.

Conclusion

Fear conditioning procedures have been applied extensively as a model for the acquisition of (clinical) fears and anxiety. In this chapter, we described the fear conditioning model and evaluated its external validity based on three validity criteria: face validity, construct validity and predictive validity. The fear conditioning model shows sufficient face validity and allows for further increasing of the similarities between the fear conditioning model and clinical anxiety by including technologies such as virtual reality. Some critiques have been formulated with regard to whether the (etiological) processes that underlie the fear conditioning model are the same as those at work in clinical anxiety (i.e., construct validity). In particular, the simple fear acquisition model, as proposed by Watson, might be insufficient to explain why some individuals develop an anxiety disorders and others do not. We discussed how modern learning approaches have addressed these criticisms by, amongst other things, taking into account contextual variables before, during or after the conditioning experience. Furthermore, the use of more complex conditioning procedures might add to the construct validity of the fear conditioning model by mimicking additional processes at play in anxiety disorders. In the section on predictive validity, we discussed that environmental and individual-level factors that decrease and increase fear after aversive experiences in the lab also do so in real life. In conclusion, the fear conditioning approach allows to investigate the acquisition of fear under highly controlled circumstances and makes it possible to identify the exact (learning) mechanisms involved in the etiology of anxiety disorders. This knowledge can provide meaningful directions in how to prevent and treat (clinical) anxiety.

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